UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/088,856	03/21/2002	Andrew Austen Mortlock	Z70598-1	6741

28120 7590 12/30/2004

ROPES & GRAY LLP
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
TRUONG, TAMTHOM NGO	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 12/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/088,856	MORTLOCK ET AL.	
	Examiner	Art Unit	
	Tamthom N. Truong	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-13,18,21-27 and 29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-13,18,21-27 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment of 08-13-04 has been fully considered. Claims 2, 3, 14-17, 19, 20, 28 and 30 have been cancelled, and therefore, the rejections for said claims have been rendered moot. The deletion of "cycloalkynyl", and the insertion of the definition for "polar group" have obviated the previous 112/2nd rejection for said terms. Clarification for claims 9, 10, 12, and 23 has also rendered moot the previous 112/2nd rejection for said claims. The enablement rejection for the limitation of "cycloalkynyl" has also been obviated by the deletion of said limitation.

Correction of informalities in the specification and claims (e.g., unmatched parenthesis, and misspelled words) has obviated the previous "Objections".

However, the amended claim 26 still has not overcome the previous 112/2nd rejection. Also, new issues of 112/1st and 2nd paragraphs are noted. Although the amended claims have obviated the previous 102 rejection, they are still obvious in view of Uckun et. al. and Myers et. al. Therefore, the following rejections are presented for pending claims 1, 4-13, 18, 21-27, and 29.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 1, 4-13, 18, 21-27, and 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following rejections apply:

a. Claim 1 recites the phrase "may be optionally substituted" (e.g., following the limitation of "...substituents on R^5", and "...group in R^{70}", which renders indefinite metes and bounds to the claim because a conditional phrase followed by another conditional phrase makes it uncertain regarding whether or not there is any substitution on a group.

b. Claims 4-13, 18, 21-27, and 29 are rejected as being dependent on claim 1 for the limitations of R^5 and R^{70} which "may be optionally substituted".

c. Claim 1 recites R^{80} which is defined as "a substituent of at least 4 atoms comprising one or more..." which has indefinite metes and bounds because moieties such as halo, cyano, carboxy and amino do not have 4 atoms. Thus, it is unclear if those moieties are substituents on other groups, or if they can be a single substituent represented by R^{80} on the pyridinyl, pyrimidinyl or pyrazinyl ring.

d. Claim 1, in the definition of R^1-R^4, the phrase "where the optional substituents comprise at least one functional group" give indefinite metes and bounds to the "optional substituents" because it is not clear how many functional groups are in a particular substituent.

e. Claim 1 recites the broad recitation "prodrug", and the claim also recites "ester, amide" which is the narrower statement of the range/limitation. A broad range or

limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in Ex parte Wu, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of Ex parte Steigewald, 131 USPQ 74 (Bd. App. 1961); Ex parte Hall, 83 USPQ 38 (Bd. App. 1948); and Ex parte Hasche, 86 USPQ 481 (Bd. App. 1949).

f. Claims 4-13, 18, 21-27, and 29 are rejected as being dependent on claim 1 for the limitations of R^1-R^4 and R^{80}.

g. Claim 8 appears to broaden the scope of claims 1, 4, 5 and 6 because it recites the limitation of "$R^2$and R^3comprises a chain of at least 3 optionally substituted carbon atoms..." which has a scope beyond that of claims 1, 4, 5 and 6.

h. Claim 26 is indefinite for reciting the limitation of "converting a group $R^{1'}$, $R^{2''}$, $R^{3''}$, $R^{4'}$to a group of R^1, R^2, R^3 or R^4 respectively". If $R^{1'}$, $R^{2''}$, $R^{3''}$, $R^{4'}$ are "equivalent" to a group of R^1, R^2, R^3 or R^4, then it is not understood why they would need to be converted. Also, the claim recites the limitation, "precursor thereof", which has indefinite metes and bounds because it is unclear as to the structure of such a precursor.

i. Claim 25 recites a "phosphate prodrug" which has indefinite metes and bounds because it is unclear as to the location of the phosphate group on the quinazoline ring.

j. Claim 27 is unclear as to the intended diseases to be treated.

Claim Rejections - 35 USC § 112 First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. **Lack Written Description:** Claim 9 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 9 has been amended to recite specific polar groups; however, said groups are not mentioned in the specification or the original claims. Therefore, claim 9 lacks written description.

3. **Enablement:** Claim 27 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in the determination of an enabling

disclosure:

(1) The breadth of the claim;

(2) The amount of direction or guidance presented;

(3) The state of the prior art;

(4) The relative skill of those in the art;

(5) The predictability or unpredictability of the art;

(6) The quantity of experimentation necessary;

[See Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int., 1986); also In re Wands, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)].

The breadth of the claim: Claim 27 recites: "A method for inhibiting aurora2 kinase in a warm blooded animal, such as man, in need of such treatment,....", which vaguely covers the treatment of numerous diseases, (known and unknown presently) using a large number of quinazoline compounds.

The amount of direction or guidance presented: The specification only provides in-vitro assay of the inhibition of aurora2 kinase which allegedly could inhibit cell cycle, and cell proliferation. However, only compound 6 is tested for such activity. Considering a large genus such as the instant formula (I), the activity of one compound cannot be extrapolated to the entire genus since the extensive substitution on the quinazoline ring could hinder such activity. Furthermore, from the in-vitro cell proliferation assay, it is not conclusive whether the claimed compounds could treat any diseases. For one thing, inhibiting cell proliferation essentially stops

the growth of all cell types, and not just cancerous cells. Thus, a mere showing of in-vitro activity does not sufficiently guide the skilled clinician to practice the invention in a safe manner.

The state of the prior art: As evident by the teaching of Uckun et. al. (US 6,258,820 B1), a similar set of quinazoline compounds can be used to treat leukemia. However, the disclosed genus is not as extensively substituted as the one claimed herein, and covers a limited number of compounds. Therefore, at most, following the teaching of Uckun et. al., the skilled clinician could only use a few compounds of the instant formula I in the treatment of leukemia.

The relative skill of those in the art: Even with the advanced training (e.g., Ph.D. and M.D program), the skilled clinician would still have to carry out extensive research to select any of the claimed compounds and use it to treat a disease that is not taught in the art. For each compound beyond the scope of Uckun et. al., the skilled clinician would have to determine a therapeutic index, and a pharmacokinetic profile which would be effective and safe to treat any disease other than leukemia. Such a task is not routine experimentation, and requires tremendous effort, time and resource.

The predictability or unpredictability of the art and **The quantity of experimentation necessary:** The pharmaceutical art has always been known for its unpredictabilily because in-vitro activity does not warrant in-vivo activity. Therefore, with the limited guidance provided by the specification and state of the art, the skilled clinician would have to carry out undue experimentation to apply a large number of compounds claimed herein in the treatment of any disease that is related to aurora2 kinase.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1, 4-7, 10, 12, 13 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Uckun et. al.** (US 6,258,820 B1) as applied to claims 1, 4-7, 10, 12, 13 and 29 above, and further in view of **Myers et. al.** (US 5,721,237).

On columns 29 and 30, Uckun et. al. disclose compound P-150 which is analogous to a compound of the instant formula I with the following substituents:

i. R^5 is formula (ii); R^{80} is $-X^{13}R^{100}$ (or sub group (e)) wherein X^{13} is –O-, and R^{100} is hydrogen (or R^{80} is –OH);

ii. R^{81} is hydrogen;

iii. R^1 and R^4, each represents hydrogen (or $-X^1R^9$ wherein X^1 is a bond, and R^9 is hydrogen);

iv. R^2 and R^3, each represents $-X^1R^9$ wherein X^1 is –O-, and R^9 is an alkyl group.

Compound P-150 differs from the claimed compound by having the pyridinyl ring substituted with –OH at the 3rd position, and not at the 5th position. However, such a difference can be overcome by the teaching of Myers et. al. (US'237).

On columns 3 and 4, Myers et. al. disclose a generic quinazoline formula substituted with –X(ring A) wherein (ring A) can be a monocyclic aryl group which includes pyridyl, pyrazinyl, and pyrimidinyl (corresponding to the instant formulae (i)-(v)). Said ring can be substituted by a group R (up to three substituents). Note, R can be anywhere on (ring A), thus, the position of R does not change the activity of the compound.

Because both Uckun's and Myers' compounds can treat cancer or selectively regulate cell growth, one of the ordinary skill in the art would have been motivated to modify the Uckun's compound by changing the position of the substituent on the pyridyl ring. Such a change would still maintain the same biological activity, and thus, would be within the level of the skilled chemist to modify.

Therefore, at the time of the invention, it would have been obvious to modify the compound of Uckun et. al. in view of Myers et. al.

5. Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Uckun et. al. (US'820) as applied to claim 25 above, and further in view of Myers et. al. (US'237).

On column 10, Uckun et. al. disclose Scheme 2 showing the reaction of 6,7-dimethoxy-4-Cl-quinazoline with H_2N-phenyl$(R)_n$. The starting material of 6,7-dimethoxy-4-Cl-quinazoline corresponds to the instant formula (VII) while the starting material of H_2N-phenyl$(R)_n$ corresponds to the instant formula (VIII). Uckun's Scheme 2 differs from the claimed process

by having a phenyl group in the second starting material. However, such a difference is within the level of the skilled chemist to modify by using H_2N-pyridinyl$(R)_n$. Note, the preparation of compound P-150 goes back to Example 1 (see column 28, Example 5). Thus, it would have been obvious to one skilled in the art to use the appropriate H_2N-pyridinyl$(R)_n$ in place of the substituted aniline.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tamthom N. Truong whose telephone number is 571-272-0676. The examiner can normally be reached on M-F (10:00-6:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

***

12-17-04

Tamthom N. Truong
Examiner
Art Unit 1624

JAMES O. WILSON
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600